REMARKS

Claims 33, 38-40, 87, 89, 92, 101, 103-107 and 109-122 are currently pending. Claims 33, 118 and 120 have been amended to recite the specific mutation of previously pending claim 34. Claim 34 has been canceled.

I. Claim Objections

Claim 107 is objected to for reciting the phrase "any one of claim 33." Claim 107 has been amended to delete the words "any one of" before "claim 33." Therefore, Applicants respectfully request that the objection be withdrawn.

II. Obviousness-Type Double Patenting Rejection

A. U.S. Patent No. 7,169,766.

Claims 33-34, 39-40, 89, 92, 101, 103-107 and 109-122 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 15 and 16 of U.S. Patent No. 7,169,766 ("the '766 patent") in view of M. Arens, J. Clin. Virology, 22: 11-29 (2001) ("Arens").

As presently amended, instant claim 33 recites a method of treating a HCV infection in a host with a 2'-C-branched pyrimidine nucleoside, identifying viral resistance to 2'-C-branched pyrimidine nucleoside in the host, and administering a second anti-HCV agent which does not induce the same resistance-conferring mutation in the virus as the 2'-C-branched pyrimidine nucleoside. The instant amendment incorporates the following limitation from previously pending claim 34, which describes the specific resistance-conferring mutation: "nucleotide 8443 (G to C) of the HCV genome or 282 Ser to Thr of the RNA polymerase region of HCV". The mutant HCV virus that results from the mutation of serine 282 to threonine in the RNA polymerase region of HCV, as recited in the instant claims, is known as the "S282T mutant."

The claims of the '766 patent recite 2'-branched triazolopyridine, imidazolopyridine, or pyrazolopyrimidine nucleosides without any teaching or suggestion of the identification of viral resistance prior to the selection and administration of a second anti-HCV agent. The claims of the '766 patent does not teach or suggest the S282T mutant.

Arens generally teaches genotyping of viruses, including HCV. However, Arens does not teach or suggest the identification of HCV resistance to 2'-C-branched nucleosides, not to mention the specific S282T mutation of the instant claims. Indeed, the Office Action admits that

Arens does not teach the specific mutation recited in the instant claims, and instead relies on "the common knowledge in the art" that mutations conferring antiviral resistance "coincide[] with the drug binding site, which is the RNA polymerase region for the claimed 2'-branched pyrimidine nucleosides." *See* Office Action, page 6.

"Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *See KSR International Co. v. Teleflex Inc.*, 82 U.S.P.Q.2d 1385, 1396 (2007), citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The Office Action's assertion of "common knowledge" is a conclusory statement because it has no factual basis for support, and it does not explain from where the alleged common knowledge arises. If the Office Action's assertion is "common knowledge," a prior art reference should be readily available to provide factual support for the Office Action's assertion. The Patent Office has not provided such evidence. The Office Action's conclusory statement alone cannot legally support a *prima facie* case of obviousness, and the double patenting rejection must be withdrawn. *See KSR*, 82 U.S.P.Q.2d at 1396.

Furthermore, even assuming, *arguendo*, that it is common knowledge to look for mutations of amino acid residues in the drug binding region of the virus (*i.e.*, the RNA polymerase region), such knowledge alone may not be enough to identify a genotype relevant to drug resistance in the virus. And, even if such a genotype is identified, it is entirely unpredictable whether the phenotypic consequence of a specific mutation will result in a mutant virus amenable to combination therapy. As demonstrated below, none of this information is predictable, nor is it taught or suggested by Arens.

Filed herewith is the Declaration of Dr. David Standring, which demonstrates that mutations conferring drug resistance in HCV are unpredictable. *See* Declaration of Dr. David Standring, ¶¶ 7-10 and 14-16. The properties of a specific mutant virus, such as its ability to replicate relative to the wild-type virus, are unpredictable. *Id.* Without the benefit of hindsight, one of ordinary skill in the art would be unable to predict whether a HCV mutant that results from drug therapy would be more or less susceptible to treatment with a second antiviral agent. Indeed, certain HCV mutant viruses that result from HCV polymerase or protease inhibitor treatment have a greater ability to replicate as compared to the original wild-type virus, making combination therapy less desirable. *Id.* at ¶¶ 14-16.

Applicants discovered that the HCV mutant that results from exposure to a 2'-C-methyl nucleoside polymerase inhibitor, the S282T mutant, is highly replication-impaired and therefore more susceptible to a second agent from another class of drugs. *Id.* at ¶¶ 14-16. The fact that the specific mutation of the claimed methods provides an advantage for combination therapy is entirely unpredictable from Arens. Thus, for at least this reason, the instant claims are not obvious over claims 15 and 16 of the '766 patent, in view of Arens.

Finally, Applicants again point out that Arens teaches away from the instant claims because it teaches that viral resistance cannot be evaluated absent knowledge of the location of a specific HCV mutation. *See Peterson,* 315 F.3d at 1331 (applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect). As discussed above, Arens provides no information about the S282T mutation of the instant claims. Arens admits to the difficulty in identifying accurate genotype data for HCV, and the unpredictability of the results of a given mutation are evidenced by the Declaration of Dr. David Standring, as discussed herein. *See* Arens, page 20. The Office Action has not provided sufficient evidence to support the allegation that one of ordinary skill in the art would have been motivated to practice the methods of the instant claims based solely on claims 15 and 16 of the '766 patent in view of Arens. Accordingly, withdrawal of the double patenting rejection is respectfully requested.

B. U.S. Patent No. 7,192,936.

Claims 33-34, 39-40, 89, 92, 101, 103-107 and 109-122 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 2-7, 9, 12-13 and 17 of U.S. Patent No. 7,192,936 ("the '936 patent") in view of Arens. (Office Action, page 7). As is the case with the claims of the '766 patent, the claims of the '936 patent do not teach or suggest the identification of viral resistance prior to the selection and administration of a second anti-HCV agent. Thus, by analogy to Applicants' arguments above with respect to Arens and the '766 patent, the instant claims are nonobvious over, and therefore patentably distinct from the claims of the '936 patent. Accordingly, withdrawal of the double patenting rejection is respectfully requested.

III. Rejection Under 35 U.S.C. § 103

A. The instant claims are not obvious over Carroll in view of Arens.

Claims 33, 34, 92, 104, 107 and 109-122 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Carroll in view of Arens, *J. Clin. Virology*, 22: 11-29 (2001) ("Arens"). (Office Action, page 9). Specifically, the Office Action alleges that the claims are obvious because Carroll teaches 2'-branched ribonucleosides in combination with second antiviral agents and Arens teaches genotyping as a part of HCV therapy. (Office Action, pages 9-10). Applicants respectfully disagree.

Claim 33 recites, *inter alia*, a method of treating a hepatitis C virus infection in a host comprising (a) administering a 2'-branched nucleoside, (b) identifying viral resistance to the 2'-branched nucleoside, and (c) administering one or more additional drugs that induce a mutation in the virus at a location other than a mutation of a nucleotide that results in a change from nucleotide 8443 (G to C) of the HCV genome or 282 Ser to Thr of the RNA polymerase region of HCV. As discussed above, 2'-C-branched nucleoside, such as the compounds recited in claim 33, induces the mutation of 282 Ser to Thr of the RNA polymerase region of HCV. The resulting mutant virus is known as the "S282T mutant."

Arens is discussed above. Carroll teaches a broad selection of antiviral compounds, including certain 2'-C-branched nucleosides. Carroll teaches combination therapy generally, including the use of interferon, but as the Office Action admits, Carroll is silent as to the step of identifying viral resistance. *See* Office Action, page 10. Neither Carroll nor Arens teach or suggest methods of treating resistant strains of HCV with the 2'-C-branched nucleosides of claim 33, nor do the references teach or suggest the S282T mutant.

The Office Action alleges that the method of claim 33 is obvious because Arens teaches a method of genotyping viruses in a treatment regimen in order to identify resistance to drug therapy. (Office Action, pages 10-11). While Arens does teach the general use of genotyping in connection with HCV therapy, Arens does not teach how to identify the specific mutant of the instant claims or whether the specific mutation would be amendable to combination therapy with another antiviral agent.

The outcome of a specific HCV mutation is entirely unpredictable. *See* Declaration of Dr. David Standring, ¶¶ 7-9 and 14-16. For example, some genotypic changes will include random variations having no connection with drug resistance. *Id.* at ¶ 7. Moreover, some

genotypic changes may impart drug resistance directly, while other changes may work by indirect mechanisms such as compensatory changes that increase the replication of a replication-deficient mutant. *Id.* None of this information is predictable, nor is it taught by Arens. *Id.*

Indeed, Arens teaches that HCV sequencing is difficult, leading to difficulty in identifying accurate genotype data for HCV. *See* Arens, page 20. The Office Action alleges that this statement mischaracterizes Arens, "because this portion of the reference pertains to determining the type or subtype of the virus and is not germane to the rejection at issue, which only concerns viral drug resistance testing." *See* Office Action, page 15. Applicants respectfully disagree, as the identification of a particular HCV strain is analogous to the identification of a HCV subtype. In other words, the identification of a specific mutant "subtype" of the virus that results from antiviral therapy is a part of the methods of the instant claims. Because Arens teaches that "it is more difficult than one might think to classify HCV strains according to subtypes," Arens supports the proposition that genotyping HCV to identify mutant strains of the virus is not routine and predictable as the Office Action alleges.

Furthermore, Arens provides no information on the phenotypic consequences of a mutation. *Id.* at ¶ 7. The properties of a specific mutant virus, such as its ability to replicate relative to the wild-type virus, are unpredictable. *Id.* A HCV mutant with greater replication fitness than the wild-type virus would not be a desirable outcome for HCV combination therapy. Indeed, some HCV mutant viruses that result from HCV polymerase or protease inhibitor treatment have a greater ability to replicate as compared to the original wild-type virus, making combination with drugs that induce these mutations therapeutically undesirable. *Id.* at ¶¶ 12-14. If the S282T mutant of the instant claims had a greater replication capacity than the wild-type virus, one skilled in the art would not have targeted this mutant for combination therapy. In other words, without the benefit of hindsight, one of ordinary skill in the art would be unable to predict whether a given mutant would be more or less susceptible to treatment with a second antiviral agent. *See In re McLaughlin*, 443 F.2d 1392, 1395 (C.C.P.A. 1972) (the use of hindsight is impermissible when evaluating the teaching of the prior art); *see also* MPEP § 2145, para. X.A.

Lastly, the unpredictability of HCV mutations discussed above provides one skilled in the art with no reasonable expectation of success, based solely on Carroll and Arens, that any specific combination therapy would succeed in treating HCV. The outcome of a specific HCV

mutation, the replication fitness of the mutant, and whether that mutant is cross-resistant to other antiviral agents, is unpredictable. Declaration of Dr. David Standring, ¶¶ 7-9, 16 and 21-22. Therefore, without the identification of specific reasons why one skilled in that art would have a reasonable expectation of success in practicing the claimed methods, a *prima facie* case of obviousness has not been made. *See KSR International Co. v. Teleflex Inc.*, 127 L.Ed.2d 705, 82 U.S.P.Q.2d 1385, 1395 (2007) (Examiner must "identify a reason that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does."); *Medichem v. Robaldo*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (reasonable expectation of success required). For these reasons, claim 33 is not obvious over Carroll in view of Arens. Because claims 92, 104, 107 and 109-122 each depend from claim 33, they are also not obvious over Carroll in view of Arens. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

B. The Declaration of Dr. David Standring is evidence of unexpected results which rebut a *prima facie* case of obviousness.

As the Patent Office is well aware, even a *prima facie* case of obviousness may be overcome with evidence of unexpected results. *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978); *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ortho-McNeil Pharmaceutical v. Mylan Laboratories*, 348 F. Supp. 2d 713, 755 (N.D. W. Va. 2004); MPEP § 2145. Therefore, even assuming, *arguendo*, that the Patent Office has stated a *prima facie* case of obviousness, Applicants submit that the data presented in the Declaration of Dr. David Standring is evidence of unexpected results sufficient to rebut a *prima facie* case of obviousness.[1]

Applicants surprisingly discovered that the HCV mutant that results from exposure to a 2'-C-methyl nucleoside polymerase inhibitor, the S282T mutant, is highly replication-impaired mutant. Declaration of Dr. David Standring, ¶¶ 14-16. Indeed, the replication capacity of the S282T mutant was found to have only 5% replication capacity as compared to the wild-type virus. *Id.* at ¶ 15. Thus, combination therapy with a drug that induces the S282T mutation would be expected to have a surprising benefit—the resulting drug-resistant virus is severely replication impaired.

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[1] As shown above, Applicants do not concede that a *prima facie* case of obviousness has been legally established.

Applicants also discovered that the S282T mutant did not demonstrate cross-resistance to other antiviral agents. If the S282T mutant were cross-resistant to other antiviral agents, combination therapy would not be desirable with a 2'-C-branched nucleoside of the instant claims. In a first experiment, a non-nucleoside HCV polymerase inhibitor was shown to have the same ability to inhibit the S282T mutant as against the wild-type virus. *Id.* at ¶ 18. In additional experiments, the S282T mutant did not demonstrate cross-resistance to Ribavirin, a drug commonly used in HCV combination therapy. *Id.* at ¶¶ 19-21. Thus, no S282T cross-resistance was observed in two different structural classes of antiviral drugs. These results provide further evidence that the use of a 2'-C-branched nucleoside in combination with a second antiviral agent that does not induce the S282T mutation would offer successful HCV therapy. In view of these unexpected results, the instant claims are not obvious. *In re May*, 574 F.2d at 1094. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

C. The instant claims are not obvious over Carroll in view of Arens and Sinko.

Claims 33-34, 39-40, 89, 92, 101, 103-107 and 109-122 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Carroll in view of Arens, further in view of Sinko *et al.* (Office Action, pages 16-17). The Office Action alleges that because Carroll teaches 2'-branched nucleosides in combination with second antiviral agents, Arens teaches genotyping of HCV, and Sinko teaches that the use of a valine ester increases the bioavailability of acyclovir, the instant claims are obvious. (*Id.*). Applicants respectfully disagree.

Carroll in view of Arens is discussed above. Sinko does not cure the defects of Carroll and Arens because Sinko merely teaches that the valine ester of acyclovir has improved oral bioavailability. Because Sinko is silent as to the genus of compounds of claim 33, viral resistance, and methods of treating resistant strains of hepatitis C virus, one of ordinary skill in the art would have no reason to combine the teachings of Carroll, Arens and Sinko to arrive at instant claim 33. *See KSR*, 82 U.S.P.Q.2d at 1395 (Examiner must "identify a reason that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does."). Thus, claim 33 is not obvious over Carroll in view of Arens and Sinko. Because claims 34, 39-40, 89, 92, 101, 103-107 and 109-122 each depend from claim 33, they

are also not obvious over Carroll in view of Arens and Sinko. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

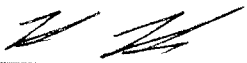
IV. Conclusion

Entry of the above amendments and remarks, and allowance of the instant claims is respectfully requested. If the Examiner believes it would be useful to advance prosecution, the Examiner is invited to telephone the undersigned at (858) 314-1200.

The fee for a Request for Continued Examination and three-month Extension of Time will be paid via EFS Web. The Commissioner is hereby authorized to charge any additional required fees, or any credits, to Jones Day Deposit Account No. 50-3013 (referencing 417451-999064).

Respectfully submitted,

Date: January 4, 2010



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